A novel hydrogen bonded motif and supramolecular patterns in the crystal structure of pyrimethamine p-hydroxy benzoate

2.1. Introduction

p-hydroxy benzoic acid is primarily known for the preparation of its esters namely parabens. Parabens are widely used as preservatives in food and pharmaceuticals. p-hydroxy benzoic acid also acts as antiseptics, antipyretic, analgesic and bacteriostatic agents. Crystal structures of p-hydroxybenzoic acid monohydrate, p-hydroxybenzoic acid and p-hydroxybenzoic acid-acetone complex (2/1), piperidinium p-hydroxybenzoate, dimorphs of hexamethyleneimini mium p-hydroxybenzoate and pyrrolidinium p-hydroxybenzoate and sodium p-hydroxybenzoate have been reported in literature. In our laboratory, co-crystal structure of 2-amino-4,6-dimethylpyrimidine–4-hydroxybenzoic acid (1/1) has been reported.

The design of supramolecular architectures, layers, ribbons, rosettes, tapes and sheets can be achieved through N-H...O and O-H...O hydrogen bonds. These interactions play an important role in crystal engineering. Besides N-H...O, O-H...O and N-H...N hydrogen bonds, the weak C-H...O hydrogen bonds also stabilize the 3-D network of structures. As discussed in previous chapter, the carboxylate group is involved in forming cyclic eight membered ring [R$_2$($2$)($8$)] motif with the pyrimidine moieties (PMN and TMP) via N-H...O hydrogen bonds. In the present study involving pyrimethamine p-hydroxybenzoate [PMNPHYBEN], the carboxylate oxygen atom as well as the phenolic OH group of the anion form a novel R$_3$($2$)($8$) hydrogen bonded ring motif with the PMN cation which self assembles in various ways leading to supramolecular architectures.
2.2. Experimental Section

2.2.1. Preparation

The compound [PMNPHYBEN] was prepared by mixing hot methanolic solution of pyrimethamine (62 mg, Shah Pharma-Chem, India) with the methanolic solution of \( p \)-hydroxybenzoic acid (34 mg, Loba Chemie) in 1:1 molar ratio. The resultant mixtures were allowed to cool at room temperature. After a few days colorless block-like crystals were obtained.

2.2.2. X-ray data collection

The X-ray data was collected using Bruker-Nonius 95mm CCD camera on \( \kappa \)-goniostat provided with graphite monochromated MoK\( \alpha \) radiation at 120K. Preliminary cell parameters were determined by collecting 45 intense and centered reflections. The recorded data (\( \theta \) range=3.0\(^\circ\) -27.5\(^\circ\)) were corrected for polarization and Lorentz effects. The absorption correction was performed by multi-scan method using SADABS.

2.2.3. Structure solution and refinement

The data set for PMNPHYBEN contained the following sets of systematic absences:

(i) Among the \( hkl \) type of reflections, \((h+k)\) odd reflections.

(ii) Among the \( h0l \) type of reflections, \( l \) odd reflections.

The first set of systematic absence revealed the C-centered lattice. The later set of systematic absence indicated the presence of \( c \) glide perpendicular to the \( b \)-axis. Hence the space group is \( C2/c \) or \( Cc \). The E-statistics showed the centrosymmetric distribution for the data set. Hence the space group \( C2/c \) was assigned. This is confirmed later by successful structure solution and refinement. The structure was solved by direct method using SHELXS97 and the structure was refined by SHELXL97. All the non-hydrogen atoms were located from a Fourier map and refined anisotropically. The H atoms were positioned geometrically and were refined using a riding model. The hydrogen atoms of the amino groups were located from
the difference Fourier map and were refined isotropically. The final R value is 0.0525 for 3855 reflections $I>2\sigma(I)$. The geometric calculations were performed by PLATON\textsuperscript{60}. The crystal data and refinement parameters are listed in Table 2.1. The fractional atomic coordinates for all the non-hydrogen atoms with the equivalent isotropic temperature factors are given in Table 2.2.

### 2.3. Results and Discussion

The asymmetric unit contains one pyrimethamine cation and a $p$-hydroxy benzoate anion (Figure 2.1). The pyrimethamine cation is protonated as it is evident from the increase in the internal angle at atom N1 [C2-N1-C6 = 121.09(12)\(^\circ\)] as compared with the neutral PMN angles [116.3(2)\(^\circ\) in molecule A and 116.1(2)\(^\circ\) in molecule B]\textsuperscript{40}. The dihedral angle between the pyrimidine and the substituted phenyl plane is 82.41(7)\(^\circ\). These values are closer to the values observed in the crystal structures of diaminopyrimidine-carboxylate salts\textsuperscript{43-52}. The torsion angle [C5-C6-C7-C8] for the compound was found to be 115.34(16) \(^\circ\). These values are close to those observed in modeling studies of dihydrofolate reductase pyrimethamine complexes\textsuperscript{63}. The length of the bond connecting the pyrimidine and phenyl ring is [C5-C9] 1.495(2) Å which is in agreement with the observed values in metoprine (1.495Å in molecule A & 1.478Å in molecule B)\textsuperscript{62}. The bond distances and angles of the non-hydrogen atoms of PMNPHYBEN are listed in Table 2.3.

#### 2.3.1. Hydrogen bonding

The protonated N1 atom and 2-amino group of the pyrimethamine cation interact with one of the carboxylate oxygen atom and the hydroxyl oxygen atom of two different $p$-hydroxy benzoate anions via N-H...O hydrogen bonds to form a novel eight membered R\(_3^2\)(8) ring motif (Motif V). The ring motif observed in this crystal structure is different from the conventional aminopyrimidinium-carboxylate R\(_2^2\)(8) ring motifs reported\textsuperscript{43-52}. The 4-amino group and unprotonated pyrimidine N3 atoms form N4-H4A...N3 base pairs [graph-set R\(_2^2\)(8)]. This type of pairing has been observed in pyrimethaminium hydrogen glutarate, pyrimethaminium formate\textsuperscript{43}, pyrimethaminium m-nitrobenzoate and $p$-nitrobenzoate\textsuperscript{45}. The
amino groups of these pairs further interact with one of the carboxylate oxygen atom (O2), forming a complementary DADA array of quadruple hydrogen bonds. The DADA array of cyclic hydrogen-bonded ring motifs can be represented by graph-set notations \( R_4^2(8) \), \( R_2^2(8) \) and \( R_3^2(8) \)^7,10,65. The oxygen-mediated synthon has been observed in the crystal structures of TMP hydrogen maleate^93 and TMP picolinate^94. The arrays are flanked on either sides by inversely related \( p \)-hydroxy benzoate anions via N-H...O hydrogen bonds forming a 20 membered \([R_4^4(20)]\) ring motif. The DADA arrays are also flanked by a 30 membered ring \([R_4^4(30)]\) motif, formed by bridging of two inversion related pyrimethaminium cations and \( p \)-hydroxybenzoate anions via C-H...O (the phenyl carbon acting as a donor to the hydroxyl oxygen atom) hydrogen bonds. All these interactions lead to supramolecular ladder like arrangement (Figure 2.2). The hydroxyl group and the carboxylate oxygens of the \( p \)-hydroxy benzoate anion form zigzag head-to-tail arrangement of supramolecular chain via O-H...O hydrogen bonds (Figure 2.3). Further the crystal structure is stabilized by stacking interactions. Stacking interactions between the pyrimidine rings are observed with perpendicular separation of 3.397Å, slip angle of 24.81º and centroid to centroid distance of 3.7427(8) Å. These observed values are in close agreement with the aromatic stacking values^76. The geometries of the hydrogen bonding interactions are given in Table 2.4.

2.4. Supplementary Materials

The atomic coordinates and the isotropic displacement parameters for all the hydrogen atoms, the anisotropic displacement parameters for all the non-hydrogen atoms, the bond distances and bond angles involving the hydrogen atom and the torsion angles for PMNPHYBEN are given in Table A 1.2.1 (Appendix 1), Table A 2.2.1(Appendix 2), Table A 3.2.1(Appendix 3) and Table A 4.2.1(Appendix 4). The least squares plane calculations (Appendix 5. txt & Table A 5.2.1) and Fo-Fc Table [PMNPHYBEN.FCF] are given in the CD attached at the end of the thesis.